WHAT IS CLAIMED IS:

1. A crystallized complex of KSP and a ligand thereof, wherein the relative structural coordinates of the amino acid residues of KSP are as set forth in Table 1 ± the root mean square deviation from the conserved backbone atoms of not more than about 2 Å.

2. The crystallized complex of Claim 1, wherein the relative structural coordinates of the amino acid residues are as set forth in Table 1 ± the root mean square deviation from the conserved backbone atoms of said amino acids of not more than about 0.5 Å.

3. The crystallized complex of Claim 1, wherein said ligand binds said KSP at a ligand binding site comprising the KSP amino acid residues 115 (M), 116(E), 117(G), 118(E), 119(R), 127(W), 130(D), 132(L), 133(A), 134(G), 136(I), 137(P), 160(L) 211(Y), 214(L), 215(E), 217(G), 218(A), 221(R) and 239(F).

4. A crystallized complex of KSP and a ligand thereof, wherein the relative structural coordinates of the amino acid residues of KSP are as set forth in Table 2 ± the root mean square deviation from the conserved backbone atoms of said amino acids of not more than about 2 Å.

5. The crystallized complex of Claim 4, wherein the relative structural coordinates of the amino acid residues are as set forth in Table 2 ± the root mean square deviation from the conserved backbone atoms of said amino acids of not more than about 0.5 Å.

6. The crystallized complex of Claim 4, wherein said ligand binds said KSP at a ligand binding site comprising the KSP amino acid residues 115 (M), 116(E), 117(G), 118(E), 119(R), 127(W), 130(D), 132(L), 133(A), 134(G), 136(I), 137(P), 160(L) 211(Y), 214(L), 215(E), 217(G), 218(A), 221(R) and 239(F).

7. A crystallized complex of KSP and a ligand thereof, wherein the relative structural coordinates of the amino acid residues of KSP are as set forth in Table 3 ± the root mean square deviation from the conserved backbone atoms of said amino acids of not more than about 2 Å.

8. The crystallized complex of Claim 7, wherein the relative structural coordinates of the amino acid residues are as set forth in Table 3 ± the root mean square deviation from the conserved backbone atoms of said amino acids of not more than about 0.5 Å.

9. The crystallized complex of Claim 7, wherein said ligand binds said KSP at a ligand binding site comprising the KSP amino acid residues 115 (M), 116(E), 117(G), 118(E), 119(R), 127(W), 130(D), 132(L), 133(A), 134(G), 136(I), 137(P), 160(L) 211(Y), 214(L), 215(E), 217(G), 218(A), 221(R) and 239(F).

10. A crystallized complex of KSP and a ligand thereof, wherein the relative structural coordinates of the amino acid residues of KSP are as set forth in Table 4 ± the root mean square deviation from the conserved backbone atoms of said amino acids of not more than about 2 Å.

11. The crystallized complex of Claim 10, wherein the relative structural coordinates of the amino acid residues are as set forth in Table 4 ± the root mean square deviation from the conserved backbone atoms of said amino acids of not more than about 0.5 Å.

12. The crystallized complex of Claim 10, wherein said ligand binds said KSP at a ligand binding site comprising the KSP amino acid residues 115 (M), 116(E), 117(G), 118(E), 119(R), 127(W), 130(D), 132(L), 133(A), 134(G), 136(I), 137(P), 160(L) 211(Y), 214(L), 215(E), 217(G), 218(A), 221(R) and 239(F).

13. A ligand binding site of a KSP protein comprising the relative structural coordinates set forth in Table 5 ± the root mean square

deviation from the backbone atoms of said amino acids is not more than about 2 Å.

14. The ligand binding site of a KSP protein according to Claim 13 comprising the relative structural coordinates set forth in Table 5 ± the root mean square deviation from the backbone atoms of said amino acids is not more than about 0.5 Å.

15. The ligand binding site of a KSP protein according to Claim 13 comprising the relative structural coordinates of the KSP amino acid residues 115 (M), 116(E), 117(G), 118(E), 119(R), 127(W), 130(D), 132(L), 133(A), 134(G), 136(I), 137(P), 160(L) 211(Y), 214(L), 215(E), 217(G), 218(A), 221(R) and 239(F) as set forth in a table selected from a group consisting of Tables 1, 2, 3 and 4, ± the root mean square deviation from the backbone atoms of said amino acids is not more than about 2 Å.

16. An agent which binds to the ligand binding site of Claim 13, wherein said agent is an inhibitor of KSP function, or a pharmaceutically acceptable salt thereof.

17. A composition comprising : (a) an agent according to Claim 16; and (b) a pharmaceutically acceptable carrier.

18. An agent, or a pharmaceutically acceptable salt thereof, which binds to five or more of the KSP amino acid residues selected from the group consisting of 115 (M), 116(E), 117(G), 118(E), 119(R), 127(W), 130(D), 132(L), 133(A), 134(G), 136(I), 137(P), 160(L) 211(Y), 214(L), 215(E), 217(G), 218(A), 221(R) and 239(F), wherein said agent is an inhibitor of KSP function.

19. A method for identifying an agent that interacts with a ligand binding site of human KSP, comprising the steps of:

(a) determining a ligand binding site of KSP from a three-dimensional model of the KSP binding site as set forth in

Table 5, ± the root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 Å; and

(b) performing computer fitting analysis to identify an agent which interacts with said ligand binding site.

20. A method for identifying an agent that interacts with a ligand binding site of human KSP, comprising the steps of:

(a) determining a ligand binding site of KSP from a three-dimensional model of KSP using the relative structural coordinates of the KSP amino acid residues 115 (M), 116(E), 117(G), 118(E), 119(R), 127(W), 130(D), 132(L), 133(A), 134(G), 136(I), 137(P), 160(L) 211(Y), 214(L), 215(E), 217(G), 218(A), 221(R) and 239(F) as set forth in a Table selected from the group of Tables 1, 2, 3 and 4, ± the root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 Å; and

(b) performing computer fitting analysis to identify an agent which interacts with said ligand binding site.

21. A method for identifying a potential inhibitor of KSP function, comprising the steps of:

(a) obtaining a three-dimensional model of a KSP binding site wherein said model contains the relative structural coordinates of the ligand binding site of KSP from a three-dimensional model of the ligand binding site as set forth in Table 5, ± the root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 Å;

(b) employing said three-dimensional model to design or select a potential inhibitor; and

(c) synthesizing or obtaining said potential inhibitor.

22. The method according to Claim 21 wherein the potential inhibitor is designed *de novo*.

23. The method of Claim 21, further comprising the steps of:

(d) contacting said potential inhibitor with KSP in the presence of a KSP binding molecule, and

(e) determining the effect the potential inhibitor has on binding between KSP and the KSP binding molecule.

24. A method for identifying a potential inhibitor of KSP function, comprising the steps of:

(a) generating a three-dimensional model of KSP using the relative structural coordinates as set forth in a table selected from Tables 1, 2, 3 and 4, ± a root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 Å;

(b) employing said three-dimensional model to design or select a potential inhibitor; and

(c) synthesizing or obtaining said potential inhibitor.

25. The method according to Claim 24 wherein the potential inhibitor is designed *de novo*.

26. The method of Claim 24, further comprising the steps of:

(d) contacting said potential inhibitor with KSP in the presence of a KSP binding molecule, and

(e) determining the effect the potential inhibitor has on binding between KSP and the KSP binding molecule.

27. The method of Claim 21, further comprising contacting the potential inhibitor with KSP in the presence of a KSP binding molecule, and determining the effect the potential inhibitor has on binding between KSP and the KSP binding molecule.

28. The method of Claim 21, further comprising contacting the potential inhibitor with KSP in the presence of one or two

KSP substrates selected from ATP and microtubules, and determining the effect the potential inhibitor has on KSP ATPase activity.

29. A potential inhibitor identified by the method of Claim 21, or a pharmaceutically acceptable salt thereof.

30. A method of identifying an inhibitor compound capable of binding to kinesin spindle protein (KSP), said method comprising:

(a) introducing protein coordinates selected from the protein coordinates provided in a table selected from Tables 1, 2, 3 and 4, ± a root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 Å, into a suitable computer program so as to define a (+)-monastrol ligand binding site conformation, wherein said program displays the three- dimensional structure of the (+)-monastrol ligand binding site;

(b) creating a three dimensional representation of the (+)-monastrol ligand binding site in said computer program;

(c) displaying and superimposing a three dimensional representation of a test compound on the three dimensional representation of the (+)-monastrol ligand binding site;

(d) assessing whether said test compound fits spatially into the (+)-monastrol ligand binding site;

(e) preparing said test compound that fits spatially into the (+)-monastrol ligand binding site;

(f) using said test compound in a biological assay for KSP function; and

(g) determining whether said test compound inhibits KSP function in said assay.

31. A process for identifying a potential anti-mitotic agent which upon binding to a human KSP inhibits cell proliferation, the process comprising the steps of:

(a) obtaining an X-ray diffraction pattern of a human kinesin spindle protein (KSP) crystal, wherein said KSP has been crystallized in the presence of a mixture of at least two potential ligands;

(d) determining whether a ligand/KSP complex is formed by comparing the electron density map calculated from the X-ray diffraction pattern of said KSP crystal to the electron density map calculated from an X-ray diffraction pattern set forth in a table selected from Table 1, 2, 3 and 4; and

(c) determining whether said ligand from said ligand/KSP complex binds to the ligand binding site of said KSP according to Claim 15, such that upon binding to KSP said ligand inhibits cell proliferation.

32. An anti-mitotic agent identified by the process according to Claim 31, or a pharmaceutically acceptable salt thereof.

33. A composition comprising: (a) an anti-mitotic agent identified according to Claim 32; and (b) a pharmaceutically acceptable carrier.

34. A method of identifying a compound that modulates the binding of a ligand to a ligand binding site of a human KSP, said method comprising: modeling test compounds that fit spatially into a KSP ligand binding site using an atomic structural model of a KSP binding site having the relative structural coordinates as set forth in a table selected from the group consisting of Tables 1, 2, 3 and 4 for the KSP amino acid residues 115 (M), 116(E), 117(G), 118(E), 119(R), 127(W), 130(D), 132(L), 133(A), 134(G), 136(I), 137(P), 160(L) 211(Y), 214(L), 215(E), 217(G), 218(A), 221(R) and 239(F), ± the root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 Å; screening the test compounds in an assay characterized by binding of a ligand to the ligand binding site; and identifying a test compound that modulates binding of said ligand to the KSP at its binding site.

35. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecular complex of a compound bound to the ligand binding site of human KSP, said three-dimensional representation comprising the structural coordinates of the KSP as set forth in a table selected from Tables 1-4 or a homologue of said molecular complex, wherein said homologue comprises a binding site that has a root mean square deviation from the backbone atoms of said KSP of not more than about 2.0 Å.

36. A method for identifying an anti-mitotic agent which upon binding to a target human KSP inhibits cell proliferation, the method comprising the steps of:

(a) obtaining a crystal of KSP, where said KSP has been crystallized while exposed to a mixture of at least two potential ligands;

(b) determining whether a ligand/KSP complex is formed in said crystal; and

(c) identifying a potential anti-mitotic agent as one that binds to said KSP at a ligand binding site having the relative structural coordinates as set forth in Table 5 ± the root mean square deviation of not more than about 2.0 Å.

37. An anti-mitotic agent identified by the method according to Claim 36, or a pharmaceutically acceptable salt thereof.

38. A composition comprising: (a) an anti-mitotic agent according to Claim 37; and (b) a pharmaceutically acceptable carrier.

39. A method for determining the three-dimensional structure of a complex of KSP with a ligand thereof, which comprises obtaining X-ray diffraction data for crystals of the complex comprising the

ligand bound to KSP at a ligand binding site; and utilizing said data to define the three-dimensional structure of the complex.

40. A method for evaluating the ability of a chemical entity to associate with a ligand binding site of human KSP or with at least a portion of the site or a complex comprising the KSP binding site; said method comprising the steps of:

(a) employing computational or experimental means to perform a fitting operation between the chemical entity and said ligand binding site of KSP having the relative structural coordinates as set forth in Table 5 ± the root mean square deviation of not more than about 2.0 Å, thereby obtaining data related to said association; and

(b) analyzing the data obtained in step (a) to determine the characteristics of the association between the chemical entity and said KSP or complex.

41. A chemical entity identified by the method of Claim 37, wherein the chemical entity is capable of interfering with the *in vivo* or *in vitro* motor activity of KSP, or a pharmaceutically acceptable salt thereof.

42. A composition comprising: (a) a chemical entity identified according to Claim 38; and (b) a pharmaceutically acceptable carrier.

43. A method for identifying a potential inhibitor of human kinesin spindle protein (KSP), the method comprising the steps of:

(a) providing a three-dimensional structure of a ligand-bound KSP as defined by atomic coordinates set forth in a table selected from a group consisting of Tables 1, 2, 3 and 4 ± the root mean square deviation of not more than about 2.0 Å;

(b) comparing the three-dimensional coordinates of the ligand when it is bound to KSP as set forth in Table 1, 2, 3 or 4 ± the root mean square deviation of not more than about 2.0 Å to the three-dimensional coordinates of a compound in a database of compound structures; and

(c) selecting from said database at least one compound that is structurally similar to said ligand when it is bound to said KSP, wherein the selected compound is a potential inhibitor of said KSP.

44. The method of Claim 43, wherein the structural similarity is determined based on the root mean square deviation in the backbone atoms of the kinesin peptide and the kinesin inhibitor.

45. A method for identifying a potential inhibitor of a human kinesin spindle protein (KSP), the method comprising the steps of:

(a) providing a three-dimensional structure of said KSP as defined by atomic coordinates set forth in a table selected from Tables 1-4 ± the root mean square deviation of not more than about 2.0 Å;

(b) employing the three-dimensional structures to design or select a potential inhibitor;

(c) synthesizing the potential inhibitor; and

(d) contacting the potential inhibitor with KSP to determine the ability of the potential inhibitor to arrest mitosis or inhibit cell proliferation.

46. A potential inhibitor identified by the method of Claim 45 or a pharmaceutically acceptable salt thereof.

47. A composition comprising : (a) the potential inhibitor identified according to Claim 46; and (b) a pharmaceutically acceptable carrier.

48. A method of identifying an inhibitor of KSP wherein the inhibitor binds to the ligand binding site according to Claim 13 which comprises determining the shift in the fluorescence of an amino acid residue at position 127 of KSP, wherein said amino acid residue is tryptophan.

49. The method according to Claim 48 which comprises the steps of:

(a) contacting KSP with the test compound and a nucleotide and measuring the fluorescence of the mixture at the peak emission wavelength for W127 in KSP;

(b) contacting KSP with a nucleotide and measuring the fluorescence of the mixture at the peak emission wavelength for W127 in KSP; and

(c) comparing the fluorescence of the mixture of KSP, the test compound and the nucleotide with the fluorescence of the mixture of KSP with the nucleotide alone.

50. An anti-mitotic agent characterized as:

(a) specifically binding to the target KSP or an analogue thereof at a ligand binding site comprising the relative structural coordinates of the KSP amino acid residues 115 (M), 116(E), 117(G), 118(E), 119(R), 127(W), 130(D), 132(L), 133(A), 134(G), 136(I), 137(P), 160(L) 211(Y), 214(L), 215(E), 217(G), 218(A), 221(R) and 239(F) according to Tables 1, 2, 3 or 4 ± a root mean square deviation from the conserved backbone atoms of said amino acids of not more than about 2.0Å; and

(b) which, upon binding to said KSP or an analogue thereof specifically inhibits said KSP or analogs biological activities.

51. A method of causing the alteration of the structural conformation of a KSP protein which comprises exposing the protein to a ligand that binds to the KSP ligand binding site as set forth in Table 5 ± the root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 Å.

52. The method according to Claim 51 wherein the KSP protein is additionally bound to a nucleotide.

53. A method of treating or preventing hyper-proliferative diseases which comprises administering to a mammal a therapeutically effective amount of a compound that binds to the KSP ligand binding site as set forth in Table 5 ± the root mean square deviation from the backbone atoms of said amino acids of not more than about 2.0 Å.

54. The method according to Claim 53 which is a method of treating or preventing cancer.

55. The method according to Claim 54 which is a method of treating cancer.

56. An isolated and substantially pure polypeptide or a fragment thereof comprising the amino acid sequence as set forth in SEQ ID NO:1.

57. The isolated polypeptide of Claim 56, wherein the polypeptide adopts the conformation of the ligand binding pocket as set forth in Table 5, ± the root mean square deviation of not more than about 2.0 Å.

58. A variant of the isolated polypeptide according to Claim 57 having at least about 80% amino acid sequence identity with the polypeptide of Claim 57, wherein the percentage identity is determined with the algorithm Gap, BASEFIT or FASTA in the Wisconsin Genetics Software Package release 7.0, using default Gap weights.

59. An active structural motif designated herein as pharmacophore model, which refers to the three-dimensional orientation of a set of features describing the physical, chemical and/or electronic environment of the active site of the human KSP, said features comprising either a hydrophobic region feature, a hydrogen bond acceptor feature and a hydrogen bond donor feature (pharmacophore model in FIG. 14A) or two hydrophobic region features and a hydrogen bond acceptor feature (pharmacophore model in FIG. 14B).

60. A method for screening and identifying potential KSP inhibitor compounds by evaluating the fit of the screened compounds to the pharmacophore models of claim 59.

61. The method of claim 60 wherein evaluating the fit is carried out via the use of a computer and a computer-readable medium.

62. A compound, comprising two hydrophobic region features and a hydrogen bond acceptor feature, wherein said features are oriented as illustrated in Figure 14B and wherein said compound inhibits the mitotic kinesin KSP;
or a pharmaceutically acceptable salt thereof.

63. A compound, comprising two hydrophobic region features and a hydrogen bond acceptor feature, wherein said features are oriented as illustrated in Figure 14B and wherein said compound fits within a ligand binding site of a kinesin spindle protein (KSP) protein, said ligand binding site comprising the relative structural coordinates set forth in Table 5 ± the root mean square deviation from the backbone atoms of said amino acids of not more than about 2 Å;
or a pharmaceutically acceptable salt thereof.

64. The compound according to Claim 63 wherein the two hydrophobic region features are independently selected from an aryl, heteroaryl and C_3-C_7-cycloalkyl, optionally substituted.

65. The compound according to Claim 63 wherein the two hydrophobic region features are independently selected from an optionally substituted phenyl.

66. The compound according to Claim 63 wherein the compound has a binding affinity for KSP of about 0.1nM to about 100nM.

67. A compound, comprising one hydrophobic region feature, a hydrogen bond donor feature and a hydrogen bond acceptor feature, wherein said

features are oriented as illustrated in Figure 14A and wherein said compound inhibits the mitotic kinesin KSP;

or a pharmaceutically acceptable salt thereof.

68. A compound, comprising one hydrophobic region feature, a hydrogen bond donor feature and a hydrogen bond acceptor feature, wherein said features are oriented as illustrated in Figure 14A and wherein said compound fits within a ligand binding site of a kinesin spindle protein (KSP) protein, said ligand binding site comprising the relative structural coordinates set forth in Table 5 ± the root mean square deviation from the backbone atoms of said amino acids of not more than about 2 Å;

or a pharmaceutically acceptable salt thereof.

69. The compound according to Claim 68 wherein the hydrophobic region feature is selected from an aryl, heteroaryl and C_3-C_7-cycloalkyl, optionally substituted.

70. The compound according to Claim 68 wherein the hydrophobic region feature is selected from an optionally substituted phenyl.

71. The compound according to Claim 68 wherein the compound has a binding affinity for KSP of about 0.1nM to about 100nM.

72. The compound according to Claim 68 wherein the compound does not comprise a 2-thioxo-1,2,3,4-tetrahydopyrimidine moiety, a dihydropyrimidine moiety or a 5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]-pyrido[3.4-b]indole-1,3(2H)-dione moiety.

73. A compound, comprising three hydrophobic region features and a hydrogen bond acceptor feature, wherein said features are spatially oriented as illustrated in Figure 16 and have the distances in Å between the features as follows

	1	2	3	4
1	-			
2	5.1±0.6	-		
3	8.5±0.7	6.9±0.7	-	
4	3.7±0.5	5.8±0.6	5.7±0.7	-

and wherein said compound inhibits the mitotic kinesin KSP;
or a pharmaceutically acceptable salt thereof.

74. The compound according to Claim 73 wherein the compound does not comprise a quinazolinone, phenothiazine, thienopyrimidinone, furanopyrimidinone, azolopyrimidinone, thiazolopyrimidine, cycloalkylpyrimidinone or triphenylmethane moiety.

SEQUENCE LISTING

<110> Merck & Co., Inc.
Buser-Doepner, Carolyn A.
Coleman, Paul J.
Cox, Christopher D.
Fraley, Mark E.
Garbaccio, Robert M.
Hartman, George D.
Heimbrook, David C.
Huber, Hans E.
Kuo, Lawrence C.
Sardana, Vinod V.
Torrent, Maricel
Youwei, Yan

<120> MITOTIC KINESIN BINDING SITE

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